ANTIBIOTICS IN ANIMAL AND POULTRY FEEDS--
A CRITICAL REVIEW OF RESEARCH

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This publication is a critical review of research on antibiotics in animal and poultry feeds. It contains discussion on uses of antibiotics in animal and poultry feeds, but this does not imply that such uses are consistent with current regulations. Antibiotics may be fed to animals or poultry only when used in compliance with appropriate State or Federal or both regulations.

CONTENTS

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Underscored numbers in parentheses refer to Literature Cited at the end of the report.

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Introduction

Antibiotics have been defined (44) as a group of soluble organic substances that are produced by microorganisms and that are characterized by the ability to inhibit, at low concentrations, the growth, activity, or multiplication of other microorganisms. Some of the antibiotics widely used in animal production are penicillin, streptomycin, bacitracin, tylosin, chlortetracycline, and oxytetracycline. The latter two antibiotics are more commonly known by their trade names, Aureomycin and Terramycin.

How do antibiotics work? Several possible modes have been proposed to account for the growth response obtained by feeding low levels of antibiotics to livestock and poultry. Three modes of action most frequently cited, each with varying degrees of support, are that antibiotics have: (a) a metabolic effect and directly affect the rate or pattern of metabolic processes in the animal; (b) a nutrient-sparing effect which may reduce the dietary requirements for certain nutrients, it has been hypothesized that antibiotics stimulate the growth of organisms that synthesize vitamins or amino acids and may suppress organisms that compete with the host animal for nutrients or they may improve the absorptive capacity of the intestinal tract; (c) a disease control effect, that is, they suppress organisms that may be responsible for the development of clinical or subclinical manifestations of disease or infections that may reduce growth rate and feed efficiency of livestock and poultry. The fact that antibiotics differing widely in chemical properties exert similar growth-promoting effects suggests that their effectiveness may be due to their action on the intestinal bacteria (44).

Why use antibiotics? In the late 1940's, research work with young chickens showed that their growth rates could be increased by adding antibiotic fermentation residues to their diets. This led to studies with other species and the response, particularly with swine, turned out to be similar to that obtained with chickens.

Considerations related to antibiotic use. The use of antibiotics as feed additives in animal production can no longer be justified solely on the basis of the well-documented benefits which accrue to the livestock producer in terms of more efficient production of animal products for human consumption. Major consideration must be given to the impact which the use of antibiotics in livestock feeds may have on human health and on ecological effects in general. The use of feed additives, such as antibiotics, is regulated by Federal and State laws with primary responsibility for their regulation assigned to the Food and Drug Administration of the Department of Health, Education, and Welfare under the provisions of the Federal Food, Drug, and Cosmetic Act.

Before FDA approves an antibiotic for use in animal feeds, the manufacturer must present adequate data to prove that (a) the antibiotic is safe for animals, (b) it is effective, i.e., when the antibiotic is used in

the manner prescribed it will produce the benefits claimed, and (c) no harmful residues are left in meat from treated animals. The main purpose of the regulations relating to antibiotic approval and use is to safeguard human health. Four main areas of potential hazard to humans are involved, three of which are related to possible residue effects. First, some humans are hypersensitive to certain antibiotics and must avoid exposure to them. Second, the possibility of toxicity of antibiotic residues must be considered. Third, no residue of a carcinogen is permitted in food derived from animals which have been treated with drugs (78). There should be no problem arising from residues in the meat of animals fed antibiotic supplements in their feed if the antibiotics have been used according to specification concerning level of intake and time of withdrawal from the feed prior to slaughter and if proper precautions have been taken during slaughter to prevent contamination of carcasses by contents of the intestinal tract.

The fourth area of concern is the possibility that, as a result of antibiotic feeding, resistant microorganisms could develop in the animal, be transferred to man and thus render ineffective the use of antibiotics in treatment of human disease. Antibiotic resistance has become a subject of growing interest to many segments of the public in recent years. Pertinent questions related to this subject would appear to be the following:

Are antibiotics still effective in animals for growth promotion? All available experimental evidence indicates that they are.

Does the presence of resistance factors in intestinal bacteria of animals constitute a threat to these animals? This question has not been answered yet. There are indications by some that a health hazard exists and by others that there is no health hazard.

Does the use of antibiotics in animal production pose a threat to human health? There are indications from some sources that such uses of antibiotics pose a potential danger to man. There is no definite evidence that the presence of antibiotic resistance in animals has resulted either in untreatable disease in man or in the increase in the total amount of drug resistance in the human population (79). Studies involving the administration of large amounts of resistant bacteria of animal origin to human volunteers have shown that these bacteria were unable to persist in the intestinal tract of humans and thus the resistance factors could not become established in the human bacterial flora (72). Thus, although transfer of antibiotic resistance from animals to man does not seem to be an important public health hazard, the subject continues to be one of great interest and its final resolution must depend on further research.

Antibiotics in Swine Production

Since about 1950, a great number of experiments on the use of antibiotics in diets of growing and finishing swine have been carried out with consistent findings of increased growth rate and improved feed efficiency. The sustained improvement in swine performance during the growing and finishing periods has been recently summarized (30). Included in this summary were the results of using a penicillin-streptomycin combination in which the average improvement for their use was 11 percent for growth rate and 5 percent for feed efficiency. The results of Tylosin use during the period 1959 to 1966 showed that improvements in rate of gain ranged from 10 to 18 percent and in feed efficiency from 3 to 7 percent. Information from other sources are suggestive that figures of 5 to 10 percent improvement in rate of gain and 3 to 5 percent improvement in feed efficiency may more accurately reflect the benefits of antibiotics in swine rations. In a survey of chlortetracycline (Aureomycin) feeding from 1950 to 1963 (74), it was found that improvements in gain were significant mainly during the first half of the period from weaning to market and that improvements in both rate and efficiency of gain were greater at higher levels of supplementation.

How antibiotics are used. It should be emphasized that all antibiotics should be fed in accordance with FDA regulations as stated by the manufacturer on the product label. In general, the levels for feeding antibiotics as recommended in the Nutrient Requirements of Swine, National Academy of Science publication 1599, 1968 (63) are as follows:

Baby pigs	44 mg./kg. of diet
Growing pigs	11-22 mg./kg. of diet
Finishing pigs	11 mg./kg. of diet

Variations in these levels may be necessary depending on the antibiotic used, the type of diet, stress factors encountered such as subclinical disease levels and other environmental conditions.

Use of antibiotics for breeding swine has not resulted in the clear-cut, consistent responses which have been obtained with growing pigs. There is a suggestion that feeding antibiotics to pregnant sows at levels of 22 to 33 mg./kg. of diet will improve birth weight, livability, and weaning weight of pigs. Antibiotics do not appear to be transferred through sows' milk and thus would not stimulate growth of nursing pigs by this route.

In a study conducted by the Battelle Memorial Institute, initial, baseline bacteriological investigations showed that both pigs and chickens harbored chlortetracycline-resistant bacteria even though the animals had no history of prior exposure to antibiotics. Subsequently, it was found that the feed ingredients used contained resistant bacteria. Following medication of the pigs with chlortetracycline (220 mg./kg. of diet) the total

numbers of enteric bacteria increased substantially. The population of chlortetracycline-resistant bacteria also increased in numbers and then stabilized at a level of about 95 percent of the total enteric bacteria count. In control pigs, the numbers of enteric bacteria decreased slightly during this time and the numbers of resistant bacteria fluctuated markedly (57).

Antibiotics and Poultry Performance

Based upon a review of the literature, 1951-1969, the preponderance of experimental evidence shows that antibiotics enhance the growth rate and feed efficiency of poultry.

Streptomycin and Aureomycin increased growth rate and feed efficiency of chicks on diets free of animal protein and on diets containing fishmeal (7). Aureomycin, streptomycin, Terramycin and penicillin stimulated the growth rate of turkey poults. Penicillin was most effective at 5 mg./kg. of diet. Combinations of antibiotics with penicillin gave no greater growth than penicillin alone (58). Growth stimulation of chickens was obtained by feeding Aureomycin, streptomycin, Terramycin, bacitracin, penicillin, tyrothricin and subtilin. The antibiotics were fed at levels ranging from 1.25 to 50 ppm. Penicillin gave the most consistent and slightly better growth response (33). Erythromycin or penicillin, or a combination of the two, gave an increase in growth rate during hot weather (36).

Not all experiments have indicated a real advantage from antibiotic supplementation. When the growth response obtained with virginiamycin was compared with that obtained with nine other antibiotics, only virginiamycin produced a significant growth response in all experiments (14). Consistently greater growth response was obtained with antibiotics when they were first used, or used occasionally. When fed routinely the growth response to bacitracin, penicillin, tylosin and erythromycin decreased gradually over an 18-month period (61).

More recently there have been three pertinent pieces of work concerned with the effectiveness of antibiotics in broiler feeds over long periods of time. A summary of experiments conducted over an 11-year period at the University of Wisconsin showed that no long term changes occurred in the weight responses obtained with procaine penicillin or tetracyclines. Variations were found between tests in the early part of the period and the latter part of the period for both penicillin and the tetracyclines. The response to antibiotics throughout the period ranged from 6 to 12 percent over that of the controls (32). A summary of published work on growth response of chickens for the period of 1951-1968 indicated no trend toward decreased effectiveness of the four antibiotics having the longest history of use (6). The magnitude of response to either procaine penicillin or zinc bacitracin showed there was no diminution of effect over the 16 years the antibiotics had been in continuous use on the same premises (13).

The conflict in results has led to numerous investigations of the factors that influence antibiotic response. The general conclusion can be drawn that under conditions of stress, that is, the presence of unfavorable

organisms, extremes in ambient temperature, disease, crowding and poor management, antibiotics have proved most effective. In commercial broiler production one or more of these conditions is almost invariably present.

The following statement has been taken from ***Nutrient Requirements of Poultry,*** National Academy of Science, Publication No. 1, Sixth Revised Edition, 1971.

"Since 1950 several antibiotics have become important additives in poultry feeds because they increase growth rate and efficiency of feed utilization by influencing the bacterial population of the digestive tract. Depending on the antibiotic used, 2 to 10 mg. per kg. of feed is needed to be effective." However, it is emphasized that all antibiotics in poultry rations should be fed at levels consistent with those approved in FDA regulations.

The results of studies on the effect of antibiotics on laying hen performance have been less consistent than those of growing chickens. One study has furnished a possible explanation for the variable reports (53). The findings indicate that when a hen is laying below her genetic capacity because of stress conditions or some subclinical infection, antibiotics may improve production. On the other hand, when a healthy bird is producing at or near her genetic capacity, antibiotic feeding is of little value. Other investigations have shown that high level feeding of antibiotics consistently improved egg production during extremely hot weather (34, 35).

In the study conducted by the Battelle Memorial Institute (57), it was found that chickens derived from stock having no prior history of exposure to antibiotics harbored chlortetracycline-resistant bacteria in their enteric flora. Feed ingredients, such as alfalfa, ground corn, meat meal, ground oats and soybean meal used in the rations, were found to contain chlortetracycline-resistant bacteria. It was concluded that these organisms are widely distributed in nature and readily colonized the intestinal tracts of chickens used in this study when introduced in the feed.

Two groups of chickens fed diets medicated with either 200 g. or 25 g. chlortetracycline per ton of feed, respectively, for 146 days and sampled weekly had significantly higher percentages of chlortetracycline-resistant bacteria in their enteric flora as compared to unmedicated controls housed either with the medicated groups or separately. The differences in percentages of resistant flora between chickens fed diets medicated at these two levels were not significant.

It was demonstrated that chlortetracycline resistance could be developed in enteric bacteria by medication and could be transferred in vivo to nonresistant bacterial species. Resistance was also transferred by contaminated chicken litter and by air-borne dissemination of resistant bacteria (57).

Antibiotics in Rations of Dairy Animals

Antibiotics are presently used routinely in the vast majority of commercially prepared milk replacers and calf starters. In other words, they are a common component of feeds used in the first three months of life of most dairy calves. Their use for older animals drops very rapidly and in the case of milking cows, very few commercial rations utilize antibiotics on a routine basis. The ages at which antibiotics are heavily used correspond closely with those ages showing consistent response from including antibiotics in feed.

Antibiotics, especially Aureomycin and Terramycin, were extensively tested on dairy calves during the 1950's. As has been the case with other species of animals, benefits from the antibiotics have been most pronounced when the experimental animals were under nutritional or environmental stress. Generally, increases in weight gains of 10 to 20 lbs. were observed by feeding antibiotics during the first 8-16 weeks of life (3, 54, 75). Growth response after this age has not been nearly as marked. A continuing superiority of weight in heifers fed Aureomycin through 200 days of age was observed by Jacobson et al. (40) and Fincham and Voelker (22). This superiority was as much as 50 lbs. per head. Similarly Bartley et al. (1) reported that the weight advantage found at 6 months in heifers fed Aureomycin was maintained to 13 months but they found no further growth stimulation in the 7-13 month period. Since most of the calves on dairy farms are being raised for herd replacements and there is no evidence to suggest that this greater weight is associated with improved production as mature animals, the increased size of maturing heifers is of limited importance.

Thomas et al. (75) followed the growth pattern of control and Aureomycin supplemented calves beyond the point at which supplementation stopped. The supplemented calves had received 50 mg./day of Aureomycin from 3-60 days of age and 100 mg. daily from 61-90 days of age. Following 90 days of age none of the calves received antibiotic supplement. The expected improvement in gain of about 20 percent was observed in the supplemented calves up to the age of 90 days. Following the removal of antibiotics from daily rations, the supplemented calves gained at a considerably slower rate for 1 to 2 months. The net effect being that these heifers were of approximately the same body weight during the 6-12 month age period. The data indicate that Aureomycin stimulated appetite and rate of body gain during the period of administration but that a period of normal intake and decreased rate of gain followed removal of the supplement.

Although most of the data available on the effects of antibiotics for dairy heifers and calves have been reported on the basis of differential weight gains, the most important economic effect may, in fact, be differences in loss from sickness and disease. As pointed out above, differences in weight gain may not be of economic importance in the case of female herd replacements. However, differentials in disease losses are very real economic factors. The mortality losses among dairy calves under one year of age in better than average herds were reported as 15 to 25 percent during

the late 40's and early 50's (16, 51, 64). Furthermore, scours is one of the leading causes of death in calves and the importance of antibiotics in reducing the instance of scours in young calves has been almost universally noted. Bartley et al. (2) noted a reduction in the incidence of scours from 27 to 5 in two groups of 12 calves over a period of 12 weeks. Similarly, Thomas et al. (75) observed a reduction of 36 percent in the number of required treatments for scours in calves up to 90 days when feeding 50 to 100 mg. of Aureomycin per day.

The work of Hogue et al. (37) suggests an important interaction between the level of milk feeding and the usefulness of antibiotics. In this case the average daily gains for calves from birth to 16 weeks were 1.16 lb. and 1.06 lb. when fed a total of 350 and 175 lbs. of milk, respectively. This differential was almost eliminated by feeding chlortetracycline or Streptomycin during the 16-week period. Commercial dairymen are constantly striving to reduce the amount of milk and milk replacer required for raising dairy heifers. Presently developing systems which require the feeding of milk replacers for only 4 weeks are probably much more dependent on the inclusion of antibiotics than are more liberal milk feeding regimes, although there are no data to specifically support this point.

Veal calves are usually fed a high energy, high milk ration. Since the work of Hogue and coworkers cited above showed little effect on dairy gain from feeding of antibiotic when a high level of milk was used, it is somewhat questionable whether the elimination of antibiotics from veal feeding rations would have as great an effect on daily gain and health as has been observed with calves raised for herd replacement.

The effects of Aureomycin and Terramycin on the production and health of milking cows has received considerable attention. Very small effects or no effects have been reported for the feeding of Aureomycin in a number of university herds (8, 46, 70). Levels of about 0.1 mg./lb. of body weight were usual in these trials. Since the general disease and health level in university and experiment station herds may be different from that observed in commercial herds, antibiotics have been separately evaluated under commercial conditions. These studies, which have included thousands of cows, have shown differences in favor of antibiotic fed cows ranging from 0 up to nearly 2 lbs. of milk per day (50, 56). Since the extent of environmental, nutritional, and disease stress will vary a great deal among commercial herds, a variance in this response is not surprising. Because of the generally low response and some conflicts in the results, it is doubtful that any sizable economic benefit would be derived from generally feeding the available antibiotics to milk cows. It is also unlikely that the practice will become very widespread.

The following comments have been taken from Nutrient Requirements of Dairy Cattle, National Academy of Science publication 139, revised 1966:

> "There are indications that improved appetite, and thus greater feed consumption, is a major factor in the response to antibiotics. Improved skeletal development accompanies the increased weight

gains; at least as far as calcium is concerned, the accelerated bone growth involves a greater intake of calcium rather than a higher percentage retention (205). Antibiotic feeding does not appreciably alter the apparent digestibility of feed nutrients in the young calf. Under most circumstances, levels of 40 mg per kg of milk replacer on a dry basis, or equivalent amount of whole milk, and 20 mg per kg of starter appear to be adequate for promoting near maximal responses, although, in some experiments, higher levels have been required to induce the same results. Responses have been observed when antibiotics were fed in the starter to 16-week-old calves; thus, initial deposition of antibiotic in the rumen also stimulates growth, but this accelerated growth rate is of relatively short duration.

Some studies report that antibiotic feeding increases milk production of dairy cows slightly, whereas a number of others report no effect on milk production. Whether low-level feeding of antibiotics has any significant effect on the general health of dairy cows is questionable."

It is emphasized that the Code of Federal Regulations does not make provisions for inclusion of antibiotics in the feed to increase the productivity of lactating dairy animals. In addition, the levels of antibiotics indicated in the above quote are approximate. Permissible levels are defined in the Code of Federal Regulations.

Antibiotics and Beef Production

Several broad-spectrum antibiotics usually fed at the rate of 20 to 25 mg. per 100 kg. of liveweight per day have shown promise as feed additives for drylot cattle. Benefits are not always realized and variations in response are not fully understood, but may be related to the disease level present in the feedlot.

Generally, antibiotics are fed at about 70-100 mg./day/head. When effective, they improve feed conversion and gains presumably by:

1. Reducing the incidence of disorders in the digestive tract.
2. Reducing the incidence of liver abscesses.
3. Aiding in the maintenance of the animal's general health by control of subclinical infections.

In a majority of over 300 well-designed experiments during the past 20 years, it has been found that chlortetracycline, oxytetracycline and zinc bacitracin are the most effective antibiotics for improving the performance of beef cattle. In general, it has been agreed that maximum growth response is obtained with about 10 mg. of antibiotic per 100 lb. of body weight or 70 to 80 mg. per head per day. The response to antibiotics, however, varies with disease level, energy level in the ration, and feedlot conditions (4). When animals were fed a high-roughage growing type ration, 70 to 80 mg. of either chlortetracycline or oxytetracycline daily, gain increased an average of 9 percent and feed efficiency was improved by 8 percent.

The feeding of 70 to 80 mg. of antibiotic in high-energy fattening rations increased gains by 4 percent and reduced feed requirements by 5 percent (4).

When antibiotics are fed in conjunction with diethylstilbestrol they may counteract the slight depression in carcass quality that may result from use of stilbestrol. Antibiotics improved both gain and feed efficiency by 6 percent, stilbestrol improved them by 12 percent and 6 percent, respectively, and a combination of antibiotic and stilbestrol improved them by 17 percent and 12 percent, respectively (4).

Low levels of antibiotics have been added to cattle rations in an attempt to combat the pathogenic bacteria thought to be responsible for increased incidence of liver abscesses when cattle are fed all-concentrate rations (81). It has been reported (41) that feeding of chlortetracycline at the level of 70 mg./head/day would significantly reduce but not eliminate abscesses of liver in cattle. This finding has been confirmed by others (18, 19) who fed chlortetracycline at 70 mg. in all-concentrate milo rations. A 30 percent reduction in liver abscesses was obtained when steers on an all-concentrate ration were fed 75 to 85 mg. of chlortetracycline per head per day (26, 27).

The use of zinc bacitracin in barley rations was of benefit in reducing liver abscesses, foot rot, and founder (17). However, in another study in which bacitracin was fed at 70 to 80 mg. per head per day, in an all-concentrate ration, no control of liver abscesses was observed (28). There is apparently a high degree of association between high energy rations and lesions of the rumen wall and liver (81).

Antibiotics in Sheep Production

Research has indicated that antibiotics improve rate and efficiency of gains and reduce the number of unthrifty lambs (29). Continuous supplementation with 10 mg. chlortetracycline per pound of feed significantly increased average daily gains of commercial feedlot lambs and was highly effective in the control of enterotoxemia (42). In another study it was found that chlortetracycline at 20 ppm. significantly improved efficiency of feed conversion and weight gain on all diets. In addition, nitrogen retention was increased and dry matter digestibility was improved in those diets containing urea. The incidence of foot rot was also reduced (10). Other studies have shown that chlortetracycline did not significantly affect the nitrogen retention or digestibility of the ration (76) or that digestibility was reduced early in the trials but recovered with time (21). Increases in rate of gain and feed efficiency attributable to feeding oxytetracycline have also been reported (9, 66). Reports have also shown that growth rate (43) or both growth rate and feed efficiency (15, 25, 68) were improved by feeding oleandomycin.

In addition to improved rates of gain and feed efficiency, numerous other advantages of feeding antibiotics to sheep have been reported. Supplementing pregnant ewes with 60 mg. of chlortetracycline per head daily

for about 80 days beginning 6 weeks prior to the start of lambing substantially reduced lamb mortality. An intramuscular injection of 350 mg. of oxytetracycline per 100 lb. body weight, given to the ewes immediately after lambing reduced lamb death loss by 60 percent (60). Feeding of chlortetracycline (49) or chlortetracycline and oxytetracycline (67) reduced the incidence of enterotoxemia. Incidence of urinary calculi was reduced by feeding chlortetracycline (65) although inconsistent results were reported by other researchers (69). Feeding of hygromycin B was found to markedly reduce the incidence of tapeworm-infected livers (45). Chlortetracycline was reported as effective in reducing vibrionic infections (23, 39) and reduced abortion rate (23, 24).

Antibiotics and Fur Animal Production

The use of 3 mg. of Aureomycin or Terramycin per pound of wet feed for growing mink kits results in larger gains, longer kits, and larger, heavier pelts (80). Similar results have been observed when Biomycin, penicillin, or Auroform were administered to mink (48, 55, 59). Procaine penicillin prevented diarrhea and weight loss in mink kits that were fed for several days on tainted fish (62) and Aureomycin, Terramycin, penicillin and bacitracin help to keep feeds wholesome for longer periods of time (77).

Antibiotics and Rabbit Production

The effects of antibiotic feeding on growth and feed efficiency in rabbits have generally been nil (11, 38, 47, 52). In addition, antibiotics have no effect on semen production or quality of rabbits (5). It appears that antibiotics have been most effective in reducing mortality of rabbits and thus increasing the total production per doe (11, 12).

Antibiotics as Feed Additives for Horses

Very little recorded research has been conducted on the use of antibiotics as feed additives for horses. Daily administration of Aureomycin was found to increase growth rate of young foals (71, 73) but did not increase weight gains of weanling foals (71). Oxytetracycline however was found to have no effect on weight or body measurements of colts under one year of age (31). In general, it appears that antibiotics may be beneficial to young foals suffering from infections, digestive distrubances or other stresses (20).

Areas of Future Research with Antibiotics

In view of the concern over the possible harmful effects of feeding antibiotics to animals and poultry, there is a need for research to clearly define the advantages and disadvantages of feeding antibiotics. Specifically, extensive feeding trials are needed to update information on the efficacy of antibiotics under present day conditions and basic research is required on the mode of action of antibiotics in animals. While the growth promoting effect of antibiotics is felt to be mediated through some effect on

intestinal microflora, the mechanism is unknown. Comprehensive studies should be conducted in vivo to determine whether pathogenic organisms which acquired antibiotic resistance are as virulent as those organisms which are not resistant and whether an animal will react to antibiotic therapy if it becomes infected with organisms that are resistant.

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